REMARKS

This Amendment/Response is in response to the non-Final Office action (Unnumbered Paper) mailed 23 December 2008.

Claims 1 through 4 and 6 through 18 are pending and under the Examiner's consideration.

Claims 7, 11, 13, 14, 16 and 17 have been amended by this Amendment, and claims 10, 12, 15 and 18 are canceled without disclaiming their subject matter.

No new matter has been added.

I. Claim Rejections – 35 USC § 112

Claims 1-4 and 6-18 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.

The examiner's rejection is not proper.

The examiner did not consider the references which are incorporated in the specification by reference. In the definition section of the instant specification, the purified Leukocyte Dialysate Subfraction was described as follows:

> "[0041] The "selected immunoregulators" ("selected immunomodulators" "selected immunoamplifiers") include the purified Leukocyte Dialysate Subfraction (LDS) described by Dr. A. Arthur Gottlieb Patents (U.S. Pat. Nos. 5,100,663, 4,616,079, 4,699,898, 4,710,380, 4,778,750, 4,874,608, 5,013,546, 5,081,108, 5,093,321 which are incorporated herein by references) which is naturally derived from healthy human leukocytes, as well as purified immunologically active components of the naturally derived immunoregulators including the dipeptide tyrosylglycine (YG) and the tripeptide tyrosylglycylglycine (YGG), as well as synthetically produced YG and YGG. These regulators also include covalently modified YG and YGG, such modifications designed to stabilize or to enhance the biological activity of said regulators, as well as pharmaceutically acceptable salts, suitable for human use, of YG, YGG, and related molecules including covalently modified YG, and covalently modified YGG."

The examiner did not consider the prior art references which are incorporated in the specification by reference, and did merely argue that the subfraction encompassed a myriad of subfractions. Please note that all the U.S. Pat. Nos. 5,100,663, 4,616,079, 4,699,898, 4,710,380, 4,778,750, 4,874,608, 5,013,546, 5,081,108, 5,093,321 are incorporated in the specification by references. Please note that the information incorporated is as much a part of the application as filed as if the text was repeated in the application. See below MPEP section.

MPEP §2163.07(b) states that:

"Instead of repeating some information contained in another document, an application may attempt to incorporate the content of another document or part thereof by reference to the document in the text of the specification. The information incorporated is as much a part of the application as filed as if the text was repeated in the application, and should be treated as part of the text of the application as filed. Replacing the identified material incorporated by reference with the actual text is not new matter. See >37 CFR 1.57 and< MPEP § 608.01(p) for Office policy regarding incorporation by reference. See MPEP § 2181 for the impact of incorporation by reference on the determination of whether applicant has complied with the requirements of 35 U.S.C. 112, second paragraph when 35 U.S.C. 112, sixth paragraph is invoked."

Therefore, when considering U.S. Pat. Nos. 5,100,663, 4,616,079, 4,699,898, 4,710,380, 4,778,750, 4,874,608, 5,013,546, 5,081,108, 5,093,321, and it is further defined as being "naturally derived from healthy human leukocytes, as well as purified immunologically active components of the naturally derived immunoregulators including the dipeptide tyrosylglycine (YG) and the tripeptide tyrosylglycylglycine (YGG), as well as synthetically produced YG and YGG", the examiner's rejection is not proper.

Withdrawal of the rejection is respectfully requested.

II. Claim Rejections – 35 USC § 102

Claims 11-17 stand rejected under 35 U.S.C. 102(b) as being anticipated by Gottlieb EP '052 as evidenced by Brennan (Springer Semin Immunopathol (1998) 20: 133-147).

The examiner argued that:

"The limitations of claims 12-13 and 15-16 "wherein said patient has at least one component of Metabolic Syndrome" and wherein said component is "a proinflammatory state" necessarily read upon rheumatoid arthritis as evidenced by Brennan et al. The limitation of claim 17: "deferring the progression of a patient from the Metabolic Syndrome" reads also upon administration of YG, YGG or purified leukocyte dialysate subfraction to patients as taught by Gottlieb."

Claims 11, 14 and 17 are amended to recite "patient having Metabolic Syndrome". Claims 11, 14 and 17 as amended are not read upon rheumatoid arthritis.

Since the identical invention is not disclosed in Gottlieb EP '052, withdrawal of the rejection is respectfully requested.

III. Claim Rejections – 35 USC § 103 and Double Patenting

Claims 1-4 and 6-17 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Gottlieb EP '052 in view of Persselin (Clin Orthop Relat Res, 1991).

Claims 1-4 and 6-18 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Gottlieb '898.

Claims 1-3 and 8-16 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-4, 8 and 13 of U.S. Patent No. 4,710,380.

Claims 1-4 and 6-18 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-4, 8 and 13 of U.S. Patent No. 4,699,898.

A. The examiner improperly regarded the symptoms or diseases of the prior art references as being associated with Metabolic Syndrome.

Please note that MPEP §2142 states that:

"The key to supporting any rejection under 35 U.S.C. 103 is the clear articulation of the reason(s) why the claimed invention would have been obvious. The Supreme Court in *KSR International Co. v. Teleflex Inc.*, 550 U.S. ___, ___, 82 USPQ2d 1385, 1396 (2007) noted that the analysis supporting a rejection under 35 U.S.C. 103 should be made explicit. The Federal Circuit has stated that "rejections on obviousness cannot be sustained with mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *In re Kahn*, 441 F.3d 977, 988, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006). See also *KSR*, 550 U.S. at ___ , 82 USPQ2d at 1396 (quoting Federal Circuit statement with approval)."

Here, regarding all the rejections including the double patenting rejection, the examiner did not provide explicit analysis, and there is no clear articulation of the reason why rheumatoid arthritis, diabetes, cancer, AIDS patients, or chronic inflammation in the cited prior art references should be regarded as being associated with Metabolic Syndrome.

The examiner cites Gottlieb (EP 0230 052 A2 and U.S. Pat. No. 4,710,380) for showing the control of rheumatoid arthritis in an individual, and the examiner also cites Persselin for showing that "rheumatoid arthritis necessarily reads upon a chronic systemic inflammatory disease and that..."

The Examiner improperly assumed that, if the disease "X" causing a symptom "A" is cured by a compound, the disease "Y" causing the same symptom "A" is also cured by the same compound. The examiner confuses a medicine (or compound) merely mitigating a symptom with a medicine (or compound) treating a disease. For example, Tylenol (a medicine merely mitigating a symptom) can reduce a fever irrespective of its causes. However, for example, if the fever is caused by infection of bacteria, the fever may be treated by a specific antibiotic (i.e., a medicine treating a disease). However, if the fever is caused by virus, the specific antibiotic will not generally reduce the fever.

In other words, the examiner's reasoning is like that because the prior art discloses the treatment of the fever from the infection caused by bacteria with the antibiotic, the antibiotic will cure the fever caused by a different disease. In order to prove this conclusion, the examiner must prove that the different disease is also caused by the infection of the bacteria, or the antibiotic has a different function to cure the different disease which is not related to the infection of the bacteria. Without meeting the burden of proof, the examiner merely made the conclusory statement.

As stated before, at the time the present invention was made, there are many causes and results of inflammatory processes. The fact that the patient has Rheumatoid Arthritis does not necessarily mean that the patient has Metabolic Syndrome.

The use of immunomodulating materials was not and is not a current method of treatment of Metabolic Syndrome or any other inflammatory condition and would not be "prima facie obvious to one of ordinary skill in the art." This is especially true since there were no such individuals skilled in the art of the use of our technology.

While Dr. Arthur Gottlieb did suggest the use of this technology to treat certain diseases, there is no suggestion in his teachings of the treatment of Metabolic Syndrome, a condition which had not been completely described when some of his patents issued, much less when the applications were originally filed. Again, this is a constellation of conditions which has been designated as its own disease. As well, the blood glucose abnormality associated with Metabolic Syndrome is different than that found in Type I or Type II Diabetes Mellitus. The latter statement goes, as well, to the Examiner's statements regarding double patenting. Again, Rheumatoid Arthritis and the blood glucose abnormality in Type I and Type II Diabetes Mellitus are entirely different than that in Metabolic Syndrome.

For the foregoing reasons, there is no clear articulation of the reason(s) why the claimed invention would have been obvious.

Withdrawal of the rejection is respectfully requested.

B. The examiner raised the same rejections which had been already withdrawn.

Please note that rejection under 35 U.S.C. 103(a) as being unpatentable over Gottlieb EP '052 in view of Persselin (Clin Orthop Relat Res, 1991) was already raised and withdrawn in view of the applicant's response and the declaration filed on March 5, 2008.

For the examiner's information, the response is herein repeated.

First, the examiner failed to show that all the claim limitations were taught or suggested by the prior art.

To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). "All words in a claim must be considered in judging the patentability of that claim against the prior art." *In re Wilson*, 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970).

Here, the inventor of Gottlieb (EP 0230 052 A2 and U.S. Pat. Nos. 4,710,380 and 5,013,546) was the husband and professional colleague of the inventor of the present invention. Dr. A. Arthur Gottlieb (EP 0230 052 A2) mentions diabetes, and Gottlieb U.S. Pat. Nos. 4,710,380 mentions Type I diabetes. Even if Gottlieb (EP 0230 052 A2) does not specifically state that the diabetes is Type I diabetes, the diabetes in Gottlieb (EP 0230 052 A2) is Type I diabetes. Where diabetes is mentioned in Gottlieb (EP 0230 052 A2), it is mentioned in a list with rheumatoid arthritis, because it is an autoimmune disease and not because of any other relationship between the two. This is evidenced by other Gottlieb's patents such as U.S. Pat. Nos. 4,710,380 and 4,920,097. The examiner is taking the reference to diabetes out of proper context. The World Health Organization recognizes three main forms of diabetes: type I, type II, and gestational diabetes (occurring during pregnancy), which have some similar signs, symptoms, and consequences, but different causes and population distributions. Type I diabetes is an autoimmune disease which results in the destruction of Beta cells of the Islets of Langerhans which are located in the pancreas. The Beta cells produce insulin. Hence, their destruction results in a lack of insulin and the inability of the body to use glucose. That glucose then accumulates in the blood, resulting in elevated glucose. The elevated blood glucose of Type I diabetes is a result of hypoinsulinemia. Such individuals are typically underweight. There is no obesity associated with Type I diabetes, as there is in Type II diabetes and in the Metabolic Syndrome.

The examiner's reference to Persselin is also not proper. While Persselin's paper does refer to rheumatoid arthritis as a chronic inflammatory disease, he appears to be dealing with this disease strictly from a clinical point of view. The cause of Rheumatoid Arthritis is an autoimmune reaction in which the joints are attacked by the patient's own immune system, resulting in damage to the joints. Such destruction subsequently results in chronic inflammation from rubbing of unprotected bone. Gottlieb, in his earlier

patents discusses treatment of the autoimmune reaction, NOT the subsequent inflammation. Neither Gottlieb nor Persselin discuss a relationship or association between rheumatoid arthritis and the Metabolic Syndrome.

Claims 1-4, 6 and 7 of the present application are directed to the control of chronic inflammation associated with Metabolic syndrome. The present invention teaches that since chronic antigenic stimulation resulting from immune dysfunction leads to the inflammatory condition which is characteristic of the Metabolic Syndrome, then correction of immune dysfunction can reduce the symptoms and characteristics of the Metabolic Syndrome, and thus the factors leading to Metabolic Syndrome related diabetes mellitus and coronary heart disease. Persselin does not disclose that the cause of rheumatoid arthritis is associated with Metabolic Syndrome. As stated above, the autoimmune reaction of Rheumatoid Arthritis, results in a decrease of joint cartilage and inflammation secondary to the joint bones rubbing against each other, without protection normally provided by the cartilage. What is important for the examiner to understand is that inflammation may be caused by many things.

That is, Gottlieb, Persselin, or combination thereof did not teach in any way the treatment of chronic inflammation in an individual having Metabolic Syndrome (i.e., chronic inflammation associated with Metabolic syndrome) as claimed in the present application.

Second, please also note that the Metabolic Syndrome is a complex constellation of symptoms and conditions which tend to appear in a cluster. That it is different than other conditions has been recognized by the world medical establishment and it has been assigned its own ICD Code (International Classification of Disease), 277.7, whereas the code for Diabetes Mellitus is 250 followed by a decimal point and number specifying the different "varieties" and status of the disease. Treatment of the Metabolic Syndrome is complex and depends on what parts of the constellation of conditions are present in any given individual. The Metabolic Syndrome is not equivalent to any type of Diabetes Mellitus or obesity, although impaired glucose tolerance and obesity may well be components of the Metabolic Syndrome as it is expressed in a given individual. It must also be said that, because there is variability in the expression of the Metabolic Syndrome, other than for inflammation, there is no universal treatment that has been found to treat it. Further, it must also be said that, although members of the medical establishment has have tried, no clear treatment of the Syndrome has been found to be "obvious".
The instant application addresses an area of commonality which was discovered by extensive research into the various components of the Metabolic Syndrome and a sophisticated re-analysis of an experimental study in which immunomodulatory therapy indicated success.

It is important that the examiner recognize that just because Rheumatoid Arthritis has an inflammatory component, it is not the same as the Metabolic Syndrome. Further, the earlier Gottlieb patents addressed the treatment of autoimmune diseases such as Rheumatoid Arthritis and Type I Diabetes Mellitus, which is clearly not the type of Diabetes found in the Metabolic Syndrome. (As well, Rheumatoid Arthritis and Type I Diabetes do not lead, as a result of the course of disease, to obesity.) Further, Dr. A. Gottlieb taught in his patents that the use of the technology described in the instant application affects autoimmune diseases as well as diseases involving immune deficiency.

A careful search of Gottlieb's patents reveals that he did not teach in any way that the technology of the instant application would treat chronic inflammation. We point out again that the parenthetical list of autoimmune diseases in Dr. A. Gottlieb's patents that includes Rheumatoid Arthritis and Diabetes is a list of autoimmune diseases.

The examiner states that her search was broadened to include "impaired glucose tolerance associated with the Metabolic Syndrome." The examiner then goes on to associate Diabetes and obesity with Gottlieb's teachings about Diabetes in prior patents, saying that impaired glucose tolerance is associated with Diabetes. There are numerous conditions and reasons for impaired glucose tolerance, including Type I Diabetes which is the subject of Gottlieb's statements in prior patents. (Note that the term "Diabetes Mellitus", a term that dates to antiquity, simply refers to "sweet urine", a symptom of any number of conditions, some related only by that symptom.) The Examiner then states that giving of insulin can result in obesity and through some contorted logic, links all of the conditions and declares that what we claim (in the claims that she has not insisted be disallowed) is obvious or is present in other patents. The examiner simply is not allowed to make all of the "logical" jumps she makes, as they are not supported by the science. Further, the use of an immunomodulator to control a metabolic disease is certainly new, unique, and not obvious to anyone. Rather, it grew out of a sophisticated analysis of data collected and examined by Gottlieb and his colleagues.

The examiner improperly equated Rheumatoid Arthritis with the glucose intolerance and/or Diabetes associated with the Metabolic Syndrome. If Rheumatoid Arthritis is an autoimmune disease, then it does, as we state, fall into a similar category of diseases as Type I Diabetes Mellitus. This is the relationship discussed by Gottlieb in the prior patents cited by the examiner.

The Examiner has taken words from various sources and made improper assumptions of identity. Diabetes mellitus can be Type I Diabetes mellitus, Type II Diabetes mellitus, or Diabetes mellitus associated with the Metabolic Syndrome. To be specific:

Type I Diabetes Mellitus: an autoimmune disease which prevents production of insulin by cells of the pancreatic islets of Langerhans. It is a genetic disease with a recessive pattern of inheritance (Gottlieb, M.S and Root, H.F. Diabetes Mellitus in Twins. *Journal of the American Diabetes Association*, 17:693-704 (1968).) Type II Diabetes Mellitus is a genetic disorder with a dominant pattern of inheritance which involves failure of the end organ (for example, muscle and liver) to use insulin.

"Type II Diabetes Mellitus" associated with the Metabolic Syndrome is a general inflammatory response causing failure of the end organs to use insulin. This form of Diabetes Mellitus is not genetically inherited.

Next, the word obesity may be that associated with excess insulin or that associated with the metabolic syndrome, among other conditions, none of which are identical in cause or treatment. Taking words out of context to find reasons for rejection does not contribute to progress.

It should be also noted that we assume that both the Diabetes included by Gottlieb and the Diabetes of the Metabolic Syndrome both result in elevated blood glucose, the reason and the treatments are not the same. Further simply giving more insulin to a person with Metabolic Syndrome, as one might do to regulate the Diabetes included by

Gottlieb, would not be expected by itself to reduce blood glucose, as the end-organs which require glucose would not be able to use that insulin.

Further, just because obesity may be associated with certain non-metabolic syndrome Diabetes therapy does not mean that it is caused by the same mechanism.

The equalities that the examiner is trying to draw simply are not valid. For example, obesity can have many root causes, as can elevated blood sugar, as can chronic irritation. To form equalities across all of these is incorrect. To do so would be the same as to say that there is only one way to treat a person who is sneezing, where sneezing can be caused by a cold (viral) or, for example, by exposure to dust (a physical irritation), or by an allergic reaction. In the first case, there is no good treatment, in the second, one would put on a mask, and in the third, one would take an antihistamine. In no case would one treatment be expected to provide relief in place of the other. In the same way, no one skilled in the art would presume that Diabetes listed with Rheumatoid Arthritis and/or other autoimmune diseases would be other than Type I Diabetes. Additionally, no one skilled in the art would presume that Type I Diabetes and the impaired glucose tolerance or Diabetes of the Metabolic Syndrome are the same condition or that they would be treated in the same way. Anyone trying to treat a person with the Metabolic Syndrome in the same way as one would treat a person with Type I Diabetes would be making a serious error. The ordinary skilled person in the art would not make such presumptions.

Please note and reconsider that the declaration under 37 CFR 1.132 incorporating the applicant's reasoning with respect to the prior art references was submitted to traverse the examiner's erroneous assumptions.

The above reasoning may apply to all the examiner's rejections including the double patenting rejection.

For the foregoing reasons, the examiner's rejection is not proper.

In view of the above, all claims are deemed to be allowable and this application is believed to be in condition to be passed to issue. Reconsideration of the rejections and objections is requested. Should any questions remain unresolved, the Examiner is requested to telephone Applicant's attorney.

No fee is incurred by this Amendment.

Respectfully submitted,

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